

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

App. No. : 09/371,354 Confirmation No. 9137
Applicant : Donovan
Filed : August 10, 1999
Title : INTRAPERICARDIAL BOTULINUM TOXIN TREATMENT FOR
BRADYCARDIA

TC/A.U. : 1600/1647
Examiner : Bunner, B.E.

Docket No. : D-3108
Customer No. : 33197

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REPLY BRIEF UNDER 37 CFR 1.193(b)(1)

Dear Sir:

This REPLY BRIEF is in response to the EXAMINER'S ANSWER mailed December 11, 2003.

In maintaining the rejections, the Examiner incorrectly states that at the time of the present invention (1999), botulinum toxin had only been effective in the treatment of involuntary muscle contraction disorders, dystonias, and spasticity in focal or segmental muscle regions (e.g., Examiner's Answer, page 5).

Appellant respectfully submits that the Examiner's characterization of the state of the art is in error. For example, as of the filing date of the above-identified application, it was known that botulinum toxin was effective to treat a variety of target tissues other than muscular tissues in conditions identified by the Examiner. Such other target tissues include smooth muscle tissues (Albanese et al. (1995) European Journal of Neurology, Vol.

2 (Supp. 3):29-33); glandular tissues, such as sweat glands (U.S. Patent No. 6,683,049, which has an effective filing date of December 28, 1993); skin lesions (U.S. Patent No. 5,670,484, which has a filing date of January 12, 1995 and a priority date of May 9, 1994; and conditions associated with autonomic nerve dysfunction (U.S. Patent No. 5,766,605, filed April 15, 1994). Thus, at the time of the present invention, botulinum toxin had been shown to be effective in treating a substantial number of conditions including conditions in addition to those identified by the Examiner. Accordingly, appellant submits that the state of the art of treatment using botulinum toxin was significantly more advanced than that contended by the Examiner.

In addition, the Examiner continues to dismiss the factual evidence provided by two internationally known, well-recognized physicians in the field of cardiology and botulinum toxin therapy (Dr. Longhurst and Dr. Brin, respectively) supporting appellant's position that the specification of the above-identified application contains sufficient disclosure to allow a person of ordinary skill in the art to practice the claimed invention without undue experimentation.

Appellant submits that the Examiner has no proper basis for failing to give deference to the doctors' world-renowned stature, particularly since the doctors rely on sound and relatively straightforward scientific reasoning in analyzing the disclosure of the above-identified application. Dr. Longhurst is the head of the Department of Cardiology at the University of California, Irvine, and Dr. Brin is the Vice President, Botox®/Neurology at Allergan. Both doctors have extensive publication histories and are very well respected in the scientific community. In their Declarations, the doctors base their statements on years of professional experience and the above-noted scientific reasoning. Thus, appellant submits that the Declarations of Dr. Longhurst and Dr. Brin must be given sufficient weight so as to conclude, based on the Declarations,

that the specification of the above-identified application contains sufficient disclosure to teach a person of ordinary skill in the art to make and use the invention.

In addition, the Examiner states that Dr. Longhurst lacks credibility because Dr. Longhurst has not worked with botulinum toxins, let alone botulinum toxins to treat cardiac conditions. Appellant submits that such a position is not proper since if anyone had used botulinum toxin in treating cardiac conditions, the claimed invention may not be patentable. Dr. Longhurst's great knowledge of and long history of care and concern for the heart make him an ideal person for considering a new heart treatment and whether such a new heart treatment has been sufficiently disclosed.

The Brin Declaration has been discounted in view of the Masato et al. reference as allegedly contradicting the statements by Dr. Brin.

Appellant submits that, at least for the reasons set forth in appellant's Appeal Brief, Masato et al. actually supports the evidence provided by the Brin Declaration.

In addition, the Examiner contends that since Dr. Brin is not a cardiologist or an expert about the heart, Dr. Brin's interpretation of a sinoatrial fat pad and sinoatrial node is not valid.

Appellant submits that although Dr. Brin is not a cardiologist, Dr. Brin is a physician who has received extensive medical training, which includes human anatomy. Appellant further submits that Dr. Brin's medical training is sufficient to demonstrate that Dr. Brin has a sufficient understanding of heart anatomy to make his statement.

The Examiner further contends that the post-filing date confirmatory data presented by way of the Masato et al. reference is not predictive of the scope of the present claims since the authors use electrical stimulation to stimulate nerve fibers.

Appellant vigorously disagrees with the Examiner, and submits that it is well established in the scientific community to use electric stimulation as a means to control the electrical activity of one or more nerve cells in the body (e.g., see Ambache (1951) J. Physiol. 113:1-17; and Roth (1994) Crit Rev Biomed Eng. 22(3-4):253-305). As is well understood, electrical stimulation provides a controlled stimulus to which a researcher can evaluate experimental results. Importantly, the experiments disclosed in the Masato et al. reference utilize electrical stimulation to stimulate the same population of nerve cells that are involved in bradycardia conditions. In addition, the Masato et al. reference actually points to the clinical use of botulinum toxin to treat arrhythmias (page 253, right column, last paragraph). Thus, appellant submits that the Masato et al reference clearly supports appellant's teaching that botulinum toxin may effectively treat bradycardia when administered to a population of neurons that are present in the SA fat pad, SA node, and AV node.

The Examiner contends that undue experimentation would be required to determine the optimal dosage of botulinum toxin to administer to a patient. To support the Examiner's position, the Examiner notes that Masato et al. discloses administering between 0.71 U/kg and 1.7 U/kg of botulinum toxin type A to the dogs. The Examiner acknowledges that the range of dosages disclosed by Masato et al. overlaps with the dosages disclosed in the above-identified application.

As appellant stated in the Appeal Brief, the determination of dosage of botulinum toxin is a routine procedure determined by a physician. The particular dosage of botulinum toxin may vary depending on the type of toxin being administered. For example, 50 units of BOTOX (botulinum toxin type A, sold by Allergan, Inc.) can have a therapeutic effect similar to about 150-300 units of DYSPORT (a different botulinum toxin type A, sold by Ipsen Pharmaceuticals). Fifty units of BOTOX (a particular type of

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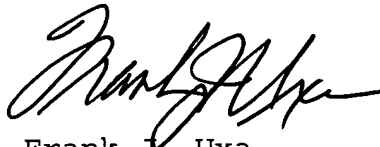
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botulinum toxin type A) is also acknowledged in the art to have a therapeutic effect similar to about 2500 to 5000 units of botulinum toxin type B (see e.g. Carruthers, A., *Botulinum toxin type A: History and current cosmetic use in the upper face*, Dis Mon 2002 May;48(5):299-322, at page 303). Thus, appellant submits that the dosages disclosed in the above-identified application are specific, in contrast to that alleged by the Examiner.

For these additional reasons, appellant submits that the claims on appeal are properly enabled under 35 USC § 112, first paragraph.

Appellant submits that, in view of the remarks included herein and in the previously filed APPEAL BRIEF, the claims on appeal, that is claims 7, 15-17, and 37-38, are enabled under 35 USC § 112, first paragraph. Therefore, appellant respectfully requests this Honorable Board to reverse the Examiner's rejection and hold the claims on appeal allowable.

Respectfully submitted,



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